KV PHARMACEUTICAL COMPANY

October 25, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. 99D-2635; Draft Guidance for Industry on ANDA's: Blend Uniformity Analysis ("BUA")

Dear Madam/Sir:

KV Pharmaceutical Company hereby submits these comments on the above-referenced draft guidance document. A notice of the availability of the document was published in the Federal Register on August 27, 1999, at 64 Fed. Reg. 46917, inviting written comments to be submitted by October 26, 1999.

The draft BUA guidance document for ANDAs raises a number of issues regarding the scope of BUA requirements which are not - but should be - addressed in the guidance. One of the most significant issues raised by the draft guidance is whether the guidance is intended to be consistent with the long-standing FDA interpretation of the cGMP requirements for in process tests in the area of blend uniformity or, instead, reflects a new, previously unannounced, and still-unarticulated agency policy in this area.

Historically, when BUA has been applicable to a product, it has been required to be conducted routinely on commercial batches only until a sufficient number have been produced to enable statistically based trend and variability analyses to conclude, with a high degree of confidence, that the procedures employed and the controls applied are adequate to assure blend uniformity. Typically, such conclusions have been accepted by the agency - in the context of both cGMP inspections and supplemental NDA/ANDA reviews - on the basis of the manufacturing and testing history of between 10 and 20 batches, in addition to the data from scale-up batches and process validation testing. Checks on the continued validity of this conclusion, as well as the continued robustness of other aspects of the approved manufacturing processes, are performed in the context of regular process re-validation studies. The long-standing agency acceptance of this approach has enabled the elimination of extensive and time-consuming routine blend uniformity tests which, over time, only become more and more redundant and pointless once the robustness of the applicable blend processes has been established.

The draft guidance does not state that the agency intends to change this long-standing approach to BUA, nor does it contain any information which would suggest a need or rationale for any change. However, by failing to include in the guidance a description of the well-established criteria currently applicable in assessing requests to curtail BUA for particular approved products, the draft guidance appears to open the door inappropriately for new and *ad hoc* requirements to be applied by individual reviewers and divisions. If the agency now intends to follow - or allow individual reviewers or reviewing divisions to follow - a different approach, this should be clearly stated by the agency and the rationale for such change should be articulated so that interested parties can

99D-2635

C9

2503 South Hanley Road, St. Louis, Missouri 63144-2555 (314) 645-6600

Whether or not a change in cGMP or ANDA review policy is intended to be signaled by the draft BUA guidance, a guidance document on BUA would be substantially incomplete without including specific guidance on the type and extent of experience and data that is regarded by the agency as adequate to support the termination of routine BUA testing. This draft provides no guidance at all on this singularly pivotal issue.

Finally, we are concerned that the current guidance, by its terms, applies solely to ANDA applicants. There is nothing about the issues involved in BUA testing, either from a cGMP or new drug product approval perspective, which turns on whether the product involved is the subject of an abbreviated or "full" new drug application. For this reason, we question whether it makes sense at all for the agency to finalize the draft in its present form and whether, instead, the agency should not be approaching these issues on a more global basis so that proper standards are articulated and applied consistently for both ANDA and NDA applicants.

Sincerely,

KV Pharmaceutical Company

Eric Moyerman.

Eric Moyerman
Vice President
Pharmaceutical Division

FedEx USA Airbill FedEx Tracking Number 8135 9433 8480

Form ID No. 0215

RECIPIENT: PEEL HERE

1 From This portion can be removed for Recipient's records. 813594338480

Date 10/25/99 FedEx Tracking Number

Sender's Name ERIC MOYERMAN Phone 314 645-6600

Company K V PHARMACEUTICAL

Address 2303 SCHUETZ RD Dept./Floor/Suite/Room

City SAINT LOUIS State MO ZIP 63146

2 Your Internal Billing Reference

3 To

Recipient's Name DOCKETS MANAGEMENT BRANCH (HFA 305) Phone

Company FOOD & DRUG ADMINISTRATION

Address 5630 FISHER LANE Rm 1061

We cannot deliver to P.O. boxes or P.O. ZIP codes. Dept./Floor/Suite/Room

To "HOLD" at FedEx location, print FedEx address here.

City ROCKVILLE State MD ZIP 20852

4a Express Package Service — *Packages up to 150 lbs.* Delivery commitment may be later in some areas.

- [ ] FedEx Priority Overnight — Next business morning
- [X] FedEx Standard Overnight — Next business afternoon
- [ ] FedEx First Overnight — Earliest next business morning delivery to select locations
- [ ] FedEx 2Day* — Second business day
- [ ] FedEx Express Saver* — Third business day

* FedEx Letter Rate not available. Minimum charge: One-pound rate

4b Express Freight Service — *Packages over 150 lbs.* Delivery commitment may be later in some areas.

- [ ] FedEx 1Day Freight* — Next business day
- [ ] FedEx 2Day Freight — Second business day
- [ ] FedEx 3Day Freight — Third business day

* Call for Confirmation: _____

5 Packaging — * Declared value limit $500

- [X] FedEx Letter*
- [ ] FedEx Pak*
- [ ] Other Pkg. — Includes FedEx Box, FedEx Tube, and customer pkg.

6 Special Handling

- [ ] **Saturday Delivery** — Available for FedEx Priority Overnight and FedEx 2Day to select ZIP codes
- [ ] **Sunday Delivery** — Available for FedEx Priority Overnight to select ZIP codes
- [ ] **HOLD Weekday** at FedEx Location — Not available with FedEx First Overnight
- [ ] **HOLD Saturday** at FedEx Location — Available for FedEx Priority Overnight and FedEx 2Day to select locations

Does this shipment contain dangerous goods? One box must be checked.

- [X] No
- [ ] Yes — As per attached Shipper's Declaration
- [ ] Yes — Shipper's Declaration not required
- [ ] Dry Ice — Dry Ice, 9, UN 1845 ____ x ____ kg

Dangerous Goods cannot be shipped in FedEx packaging.

- [ ] Cargo Aircraft Only

7 Payment *Bill to:* Enter FedEx Acct. No. or Credit Card No. below

- [ ] Obtain Recip. Acct. No
- [X] Sender — Acct. No. in Section 1 will be billed.
- [ ] Recipient
- [ ] Third Party
- [ ] Credit Card
- [ ] Cash/Check

Total Packages | Total Weight | Total Charges

Credit Card Auth.

†Our liability is limited to $100 unless you declare a higher value. See the *FedEx Service Guide* for details.

8 Release Signature *Sign to authorize delivery without obtaining signature.*

By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.

Questions? Call 1·800·Go·FedEx® (800-463-3339)

Visit our Web site at www.fedex.com

SRP 699 • Rev. Date 11/98 • Part #154813S • © 1994-98 FedEx • PRINTED IN U.S.A.

359

8135 9433 8480

[redacted]

FedEx STANDARD OVERNIGHT TUE

Emp# 39671 25OCT99

TRK# 8135 9433 8480 FORM 0215

Deliver By: 26OCT99 AA

20852 -MD-US IAD NJ EDGA